REVIEW ARTICLE

Partial breast irradiation: a review of techniques and indications

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ABSTRACT. The addition of whole-breast external beam radiotherapy (EBRT) to breast-conserving surgery results in a significant reduction in the risk of death due to breast cancer, but this may be offset by an increase in deaths from other causes and toxicity to surrounding organs. Because of this, and with a view to patterns of local recurrence, irradiation of the tumour bed has been explored in selected patients with early breast cancer using a variety of radiotherapeutic modalities. This review article explores the treatment options for partial breast irradiation and examines their role within the field of breast cancer treatment.

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Radiology

Breast-conserving surgery is a proven alternative to mastectomy in patients with early-stage breast cancer, offering equivalent disease-free and overall survival [1–3]. The addition of whole-breast external beam radiotherapy (EBRT) to breast-conserving surgery results in a significant reduction in the risk of death due to breast cancer, but this is offset by an increase in deaths due to other causes [3]. However, this increase in mortality was seen with a follow-up of over 20 years and as such reflects the use of radiotherapy techniques that have since been replaced with more sophisticated methods that allow more sparing of normal tissue. Therefore, we might not observe similar late toxicities when current EBRT techniques are analysed 20 years from now. When systemic therapy such as tamoxifen is combined with breast-conserving treatment, the risk of ipsilateral breast recurrence and distant metastases is further reduced [4]. Breast-conserving surgery is often preferred by patients, as it provides improved cosmesis and decreased psychological trauma. In some areas, however, eligible patients may not receive breast-conserving therapy for a variety of physician- and patient-based reasons [5]. Whole-breast radiotherapy (WBRT) takes 3–7 weeks with treatment once daily. This can be difficult to achieve, especially in communities where the cancer centre serves a large geographical area.

Conventional WBRT has changed very little over the years; it is generally delivered using two tangential beams (Figure 1), typically of 6 MV photons. Traditionally, the dose was defined using one axial contour in the centre of the field; however, more centres are now using CT planning to ensure greater homogeneity across the breast volume, while optimising avoidance of normal tissue. Late toxicities of WBRT can include radiation pneumonitis, osteonecrosis of the ribs

and cardiovascular complications. These cardiovascular incidents could contribute to the increased all-cause mortality in radiotherapy patients seen in studies, although, again, these may be decreased with modern radiotherapy techniques [2, 3, 6].

In disease sites elsewhere in the body, technological developments have allowed a move towards image-based target definition with sculpting of fields around anatomically defined target volumes. Therefore, the possibility of irradiating the tumour bed rather than the whole breast in patients with early breast cancer has been explored. Some investigators would choose not to treat these patients, but radiation has been shown to decrease local recurrence in this situation [4]. In trials of lumpectomy with or without WBRT, most local recurrences in the non-irradiated arm occurred in the tumour bed with a recurrence rate elsewhere of 1.5–3.5% [1, 2, 7, 8]. Pathological examination of mastectomy specimens from patients with small unifocal invasive carcinomas has shown that invasive tumour foci are generally confined to a narrow margin around the invasive tumour component [9, 10].

Therefore, partial breast irradiation (PBI) is being investigated as an alternative treatment for selected patients with early-stage breast cancer. The use of PBI may improve the underutilisation of breast-conserving treatment by decreasing the time, cost and inconvenience of WBRT and improving the quality of life of patients. Case selection is the paramount factor in ensuring the suitability of a patient for PBI, combining pre-operative and surgical tumour staging to exclude patients at a higher risk of locoregional recurrence.

A number of methods of PBI exist. Using photons or electrons, a single treatment can be given at the time of surgery [11–13]. EBRT can be used to deliver a partial breast treatment with electrons, conventional beam approaches or intensity-modulated radiotherapy (IMRT) techniques. Brachytherapy can be delivered using low dose rate (LDR), pulsed dose rate (PDR) and high dose

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Figure 1. (a) Axial and (b) sagittal CT images demonstrating the isodose curves generated for a parallel opposed pair of 6 MV photon beams with wedges for whole breast radiotherapy of the right breast.

rate (HDR) isotopes delivered by way of a single catheter or multiple catheter implants. Many of the data surrounding these different modalities are from Phase I or II trials, but increasing numbers of patients are being enrolled into Phase III randomised trials.

Radiobiology

Given the heterogeneity of treatment modalities and fractionation regimens for PBI, an understanding of the current data regarding the radiobiology of breast cancer has become imperative for the clinical oncologist. Dose response in breast cancer, especially in the adjuvant setting with subclinical disease only, has been difficult to study. Therefore, the radiobiology of breast cancer is largely derived from the study of relapse patterns and toxicity within clinical trials employing varied radiotherapy schemes. The most instructional experience comes from the EORTC boost studies, which have shown that delivery of a higher dose to the tumour bed significantly reduced the local recurrence rate, especially in younger age groups. However, this was at the cost of higher rates of fibrosis, particularly at higher dose levels [14, 15]. In contrast, the START A trial showed only a 0.2% gain in local control per 2 Gy dose increase, again with a corresponding rise in normal tissue toxicity. This finding suggests that there is little gain in dose escalation in situations where local control is over 95% [16].

Of more interest is the issue of fractionation. The classical assumptions regarding tumour and late tissue sensitivity to fraction size come from data on squamous cell cancers. An α - β ratio of 3 Gy is typically assumed for

normal tissues, while a ratio of 10 is assumed for tumour control. To date, two trials have looked at altered fractionation schedules for whole-breast irradiation. The START A trial in the UK randomised 2236 women to 1 of 3 fractionation schedules: 50 Gy in 25 fractions, 39 Gy in 13 fractions and 41.6 Gy in 13 fractions [16]. These fractionation schedules were chosen to be iso-effective assuming an α - β ratio of 1.8 Gy for normal tissues and of 6.0 Gy for tumour. The design of the trial is unique in that the overall treatment time was identical in the two experimental arms. Neither experimental arm showed significantly different local control from the control arm, although 39 Gy in 13 fractions showed slightly higher rates of absolute relapse than 41.6 Gy in 13 fractions. Late breast changes were scored by annual photographs that were blinded to the treatment arm. The α - β ratio for late-responding breast tissue was determined to be 3.4 Gy, while the α - β ratio for local relapse was 4.6 Gy. The similarity of these two estimates is striking. This low α - β ratio means that small changes in fraction size may produce relatively large changes in the effect of radiotherapy within breast tissues. Similarly, Whelan et al [17] randomised over 1200 women to either a conventional 50 Gy course of radiotherapy or 42.5 Gy in 16 fractions. The authors demonstrated almost identical local control and cosmesis in the two arms. This data set also supports a low α - β ratio (around 3 Gy) for tumour control in breast cancer.

Although the various fractionation schedules for PBI may seem to underdose the target volume when assuming an α - β ratio of 10 Gy for tumour control, the same schedules are typically comparable to standard WBRT when an α - β ratio of 3–4 Gy is assumed. One

additional factor of relevance is the relative biological effectiveness (RBE) of low-energy photons, as used in the intra-operative TARGIT method described below. An RBE of 1.5 at a depth of 10 mm and of 2.0 at 25 mm is estimated [11, 18]. This estimate of RBE may increase tumour control probability and compensate for lower total doses; however, this estimate is made assuming an α - β ratio of 10 Gy for tumour cells. Using the lower estimates of 3–4 Gy, the RBE would be 0.92 at the applicator surface and 1.45 at 10 mm [19]. These calculations were made assuming a relatively fast half-time for repair of tissue damage (15 min); if this is in fact longer, then the RBE would be higher.

It is important to remember that, although an increased fraction size may be determined as within tolerance for late-responding normal breast tissue, and could possibly be beneficial for breast tumour treatment, other late-responding fraction-sensitive normal tissues, such as the heart and lungs, will be receiving incidental radiation at a higher dose per fraction. The clinical consequences of receiving incidental radiation at a higher dose per fraction are as yet unknown, especially in the paradigm of having also received potentially cardiotoxic chemotherapy. These tissues may behave like normal breast tissue, in which the effects of a larger fraction size can be counterbalanced by using a lower total dose (such as in the START A and B trials), but the full data on this will not be available until 15–20 years of follow-up have passed.

Intra-operative techniques

With increased waiting times for breast cancer radiotherapy contributing to poorer outcomes [20–23], single-fraction intra-operative radiotherapy techniques that allow rapid treatment without the delay and inconvenience of the patient returning for daily radiotherapy treatments are attractive. Following wide local excision and sentinel lymph node sampling, the radiotherapy applicator is placed directly onto the tumour bed. The radiotherapy can be delivered using electrons (ELIOT: electron beam intra-operative radiation therapy [12]), photons (TARGIT: targeted intra-operative radiotherapy [11], intrabeam [13]) or HDR brachytherapy (HAM: Harrison Anderson Mick applicator [24]) (see Table 1).

The radiation dose can be delivered to the operative site accurately and quickly. With intra-operative techniques, geometric miss may be caused by poor annealing of the surface of the cavity to the applicator. The chance of this happening can be lessened by the utilisation of imaging, such as ultrasound or fluoroscopy, to confirm annealing before the dose is delivered.

Following the initial capital outlay for a treatment machine, intra-operative techniques are cheaper than other PBI techniques [11], requiring less treatment machine time per patient and lower physicist and physician time. Time is also saved on the linear accelerator, potentially allowing waiting times to decrease. However, these cost savings may be balanced by increased operating theatre times and equipment costs. Intra-operative techniques suffer from the possible disadvantage of not knowing the final histopathology results before treatment. Therefore, some patients may be being undertreated using intra-operative radiotherapy, although there is still the potential to deliver WBRT at a later date using the intra-operative dose as a tumour bed boost. Despite the increased RBE of the 50 kV beam mentioned above, the dose at depth delivered by TARGIT is much lower than most other PBI techniques. It will be interesting to compare long-term follow-up data with other techniques as they become available.

The delivery of radiotherapy at the time of operation may take advantage of unique changes in the operative environment that cannot be achieved by other radiation methods. When surgical wound fluid was added to breast cancer cell lines *in vitro*, it stimulated cell growth and invasion [25]; however, when using surgical wound fluid from a patient who had undergone intra-operative electron therapy, these effects were not seen. This could mean that, in addition to the direct cell killing effects of radiation, intra-operative radiotherapy renders the wound environment less favourable for cell growth and invasion.

A typical electron dose is 21 Gy to the 90% isodose using 3–12 MeV electrons encompassing the tumour bed. The depth of the prescription dose, from 1.5 to 3 cm, is determined intra-operatively, and shielding of the chest wall added if required [12]. A typical photon dose is 20 Gy at the applicator surface, delivering 5–6 Gy at 1 cm in tissue using 50 kV X-rays from a spherical applicator. HDR doses of 18–20 Gy at 1 cm from the linear HAM

Table 1. Summary of studies using intraoperative partial breast irradiation

	Keshtgar, 2008 [58]	Veronesi, 2005 [27]	Beal, 2007 [24]
Number of patients	17	590	50
Radiotherapy technique	Photons 50 kV	Electrons 3–12 MeV	HDR brachytherapy 0.38 MeV
Median follow-up (months)	20	20	21
Crude in breast tumour recurrence	0	1% (n=6)	0
Cosmesis	Not reported	Not reported	Dependent on volume irradiated
Toxicity	0	3% fibrosis, 2.5% fat necrosis	Of initial 18 patients, 5 had retraction/fibrosis at 20 Gy
Notes	Patients who were unsuitable for external beam radiation were treated with “boost” only	Dose selected by earlier dose-seeking study	Dose reduced from 20 to 18 Gy owing to toxicity

HDR, high dose rate.

applicator have also been investigated. Phase I/II studies have shown favourable outcomes for intra-operative radiotherapy with low levels of local recurrence and generally low rates of acute and late toxicity [11, 13, 24, 26, 27]. Phase III randomised trials comparing intra-operative radiotherapy with WBRT are ongoing with TARGIT [28] and ELIOT [12].

External beam radiotherapy

PBI can be delivered using EBRT with electrons, IMRT or three-dimensional conformal techniques with photons or using protons (Table 2). EBRT has the advantage of being administered after surgery, thus, the full histology results are known at the time of treatment without requiring a second interventional procedure for catheter placement. In addition, all clinical oncologists have experience of EBRT, whereas only a few have experience of brachytherapy or intra-operative techniques. The dose is more homogeneous with EBRT than intra-operative or brachytherapy techniques, which may give a cosmetic advantage. This could be a disadvantage for tumour control, however, as the dose heterogeneity seen with other techniques may increase cell kill. Clinical target volume (CTV) localisation for EBRT is difficult without CT simulation, even with placement of clips in the tumour cavity. Additional margins must be added to the CTV to account for chest wall movement and patient movement, which may result in a larger irradiated volume than brachytherapy or intra-operative techniques.

There are fewer published data on accelerated partial breast irradiation (APBI) using EBRT. The only published randomised series is one of historical interest from the 1980s and shows a much higher relapse rate in the APBI group [29]. Women were randomised to WBRT or limited-field radiation using a direct electron field: 40–42.5 Gy in 8 fractions over 10 days. The overall survival in the two groups was virtually identical; however, the actuarial local relapse rate at 7 years was significantly higher (19.6%) in the limited-field group than in the WBRT group (11%). There was a significantly increased relapse rate in patients with lobular cancer in the limited-field group. This pattern was also seen in the patients with an extensive intraductal component. When these patients were excluded from the analysis, there was still a non-significant trend to a higher relapse rate in the limited-field group. This was thought to be secondary to the increased risk of geographical miss in the limited-field group, as there was no radiological method to provide cavity definition. Cosmesis was worse in the limited field group, with increased fibrosis and telangiectasia, but this may result from the treatment delivery with 8–14 MeV electrons and a high dose per fraction in these patients with decreased understanding of the radiobiology of breast cancer at that time.

More recent Phase I studies of EBRT APBI with stricter patient selection criteria and modern treatment planning techniques are showing better results with the patient both prone [30, 31] and supine [32, 33]. Prone positioning decreases the effect of chest wall movement and moves the CTV further away from critical organs such as the heart and lungs [34]. A typical dose fractionation scheme using prone EBRT PBI is 30 Gy in 5 fractions over 10

Table 2. Summary of studies using external beam partial breast irradiation

	Ribero, 1993 [29]	Formenti, 2004 [30]	Kozak, 2006 [38]	Vicini, 2003 [33]
Study period	November 1982–December 1987	June 2000–December 2003	March 2004–June 2005	August 2000–December 2002
Number of patients	708	47	20	31
Median follow-up (months)	65	18	12	10
Radiotherapy technique	8–14 MeV electrons tumour bed clinically localised (randomised against WBRT 40 Gy/15 fractions)	IMRT 43/47 patients prone tumour bed CT localised	Protons	3DCRT with photons
In breast tumour recurrence	19.6% (versus 11% for whole breast)	0	0	Not reported
Cosmesis good/excellent	"Marked telangiectasia" in 33%, "marked fibrosis" in 14%	94% patients >6 months follow-up (n=34)	89% at 6 months, 100% at 12 months	100%
Toxicity Grade 3/4	Toxicity not graded Fat necrosis 5% Breast oedema 2% Rib fractures 2%	0	Moderate or severe moist desquamation in 22%; one rib fracture	0

3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiotherapy; WBRT, whole-breast radiotherapy fractions.

days, which has equivalent biological effects for early and late toxicity [35]. PBI using a supine technique has been assessed with a variety of methods to ensure target coverage, such as active breathing control [32] or cone beam treatment verification [36], and has been shown to be technically feasible and reproducible [37] with acceptable cosmesis and toxicity [32]. A Phase I/II clinical trial of PBI using protons has shown good to excellent cosmetic outcome, but has shown high levels of early skin toxicity [38].

Brachytherapy

Post-operative APBI using brachytherapy was initially developed using interstitial implants (Table 3). These require the placement under anaesthetic of a number of needles or tubes across the tumour bed, either with a template or freehand. The treatment volume is generally the tumour cavity plus a 1–2 cm margin. The dose is custom-shaped to this treatment volume (Figure 2). The dose can be delivered using LDR brachytherapy, typically over 4–5 days, or fractionated HDR brachytherapy, typically treating twice a day for 4–5 days. The large number of catheters in an interstitial implant allows more control over skin and chest wall doses, especially with HDR dose optimisation. The dose within the tumour is more homogeneous with lots of smaller hot-spots, as compared with the one large hot-spot obtained with single-catheter techniques. However, interstitial brachytherapy requires a high level of skill and training and can be quite operator dependent. Catheter insertion will often require a second general anaesthetic.

Interstitial implants have been in use for over 10 years and published reports describe excellent results; however, these are mainly single-institution Phase I/II studies [39–46]. The largest matched-pair analysis from the William Beaumont Hospital compared 199 interstitial catheter APBI patients treated between 1980 and 1997 with 199 WBRT patients randomly selected from 709 eligible control subjects [39]. Each brachytherapy patient was matched to a WBRT patient according to multiple prognostic factors such as age, tumour size, histological grade and lymph node status. There was no significant difference in local recurrence, elsewhere failure, disease-free or overall survival. There was a significantly lower incidence of contralateral breast cancer in the brachytherapy group.

The MammoSite applicator (Hologic Inc., Marlborough, MA) was devised to allow partial breast brachytherapy to become more accessible and reproducible. It employs an HDR source at the centre of an inflatable balloon, which is placed within the surgical cavity following breast cancer resection. The balloon can be placed at the time of surgery or later when the histopathology results are available using ultrasound guidance under local anaesthetic. Treatment is delivered in an accelerated course over 1 week. The balloon is relatively simple and easy to insert and less traumatic than multicatheter interstitial brachytherapy. However, because this is a single-catheter technique, the dose distribution cannot be customised for irregular-sized cavities or adjusted to avoid chest wall or skin surfaces without compromising CTV coverage (Figure 3). This approach is also more dependent on

Table 3. Summary of studies using brachytherapy partial breast irradiation

	Arthur, 2008 [59]	Polgár, 2004 [45]	King, 2000 [43]	Vicini, 2003 [39]	Vicini, 2008 [60]
Study period	May 1997–March 2000	1996–1998	January 1992–October 1993	1993–2001	May 2002–July 2004
Number of patients	99	45	51	199	1449
Median follow-up (months)	84	81	75	65	30
Radiotherapy technique	Multicatheter interstitial (LDR or HDR)	Multicatheter interstitial (HDR)	Multicatheter (LDR and HDR)	Multicatheter interstitial (LDR and HDR)	Balloon catheter
In breast tumour recurrence	6/99, 5 year 4%	3/45, 5 year 4.4%	1/51	5/199, 5 year 1%	23/1449, 2 year 1%
Cosmesis good/excellent	Not reported	84%	75%	99%	95%
Toxicity Grade 3/4	Late Grade 3 toxicity: 18% for LDR, 4% for HDR	One Grade 3 fibrosis, one symptomatic fat necrosis	4/51 (8%)	0	10.6% symptomatic seromas, 1.5% fat necrosis

HDR, high dose rate; LDR, low dose rate.

Figure 2. (a) Interstitial breast brachytherapy applicators with (b) axial and (c) coronal CT images demonstrating the isodose pattern of the interstitial catheters and surrounding critical normal tissues.

breast size, as smaller-breasted women are likely to have more pain and toxicity following balloon insertion [47].

In the USA, approval from the Food and Drug Administration (FDA) was received for the MammoSite device in May 2002; therefore, the follow-up period using this treatment method is much shorter than for PBI techniques. Despite this paucity of long-term data, single-catheter APBI brachytherapy has been widely taken up. The results from Phase I/II studies show excellent cosmetic results in 80–97% of patients [48, 49], with a high correlation of poor cosmesis with decreased balloon to skin distance. The longest published follow-up to date shows no ipsilateral breast recurrence in 34 patients at a median follow-up of 39 months [50]. The MammoSite device has also been used in the treatment of ductal carcinoma-in-situ (DCIS) with a 2% local recurrence rate at a median follow-up of 9.5 months [51]. In the UK, intracavitary brachytherapy is being explored within the confines of a 100 patient MammoSite multi-institution Phase II study, FORUM

(feasibility of radiotherapy using MammoSite). This will enable assessment of the feasibility of the MammoSite device in the UK healthcare setting prior to possible randomised trials.

The conformation of the MammoSite catheter with dose delivery by way of a single catheter means that there is no opportunity for “dose sculpting” (conforming the dose to the PTV). For example, such sculpting could be used to decrease the dose received by the heart in situations where the balloon lies closer to the chest wall, without compromising PTV coverage. This problem may be overcome in the future with the introduction of single-entry insertion catheters with multiple channels such as the ClearPath™ catheter [52] (North American Scientific, Chatsworth, CA). A miniature X-ray source with an energy of 40–50 kVp has been developed, the Xofig Axxent (Xofig Inc., Sunnyvale, CA) [53, 54]. This source has been developed for balloon-based APBI and the dosimetry compares favourably with that delivered by a

Figure 3. Three axial CT images at different levels in the same patient demonstrating the isodose pattern of the MammoSite balloon and surrounding critical normal tissues. The image at the bottom right shows a reconstruction of the MammoSite balloon with the 100% isodose curve in red (3.4 Gy)

^{192}Ir source using the MammoSite applicator [55]. Publications at present focus on animal experiments and computerised modelling work.

It is important to assess the role of APBI in a randomised Phase III study (Table 4). The NSABP-B39 study aims to accrue 3000 patients over 2.5 years. The patients are randomised to WBRT or ABPI using multicatheter interstitial brachytherapy, single catheter balloon brachytherapy, IMRT or three-dimensional conformal radiotherapy. The study aims to assess equivalence and compare local control rates. In Europe, the GEC/ESTRO group is aiming to recruit 1170 early-stage breast cancer patients, randomising WBRT against brachytherapy APBI in a Phase III randomised multi-institution trial. The APBI arm will receive multicatheter interstitial brachytherapy using HDR or PDR [57]. The primary end point of the study is local control. The IMPORT LOW trial is a Phase III trial in the UK, which is randomising WBRT of 40 Gy in 15 fractions against PBI (40 Gy in 15 fractions) with or without low-dose WBRT (36 Gy in 15 fractions) [56]. The PBI can be delivered to a supine patient using simple IMRT techniques via two tangential fields. This enables PBI to be investigated by departments that do not have access to more complex treatment modalities.

Conclusions

The move from WBRT to PBI can be compared with the move from mastectomy to breast-conserving surgery. Breast-conserving therapy was initially felt to be rash and dangerous; however, when it was proven to be safe in the context of randomised controlled trials, the treatment paradigm shifted internationally. PBI has a place in a selected group of patients, but must be subjected to rigorous randomised study before it is deemed a mainstream alternative to WBRT. It is imperative that we enter suitable patients into trials to further investigate the role of PBI. The definition of local recurrence for these clinical trials — within the treated volume compared with other quadrants of the breast — is one that must be clearly defined when reporting the results of these trials. When using a new technology, it is important to consider not only tumour control but also normal tissue complication probability. When post-radiotherapy follow-up is short, this must be predicted using computerised dosimetry programs and radiobiological modelling. It is essential that practicality of treatment does not outweigh tumour control and normal tissue toxicity.

Table 4. Current international randomised trials comparing whole-breast radiotherapy with partial breast irradiation

	NSABP B39/RTOG 0413	GEC ESTRO	IMPORT LOW	ELIOT	TARGET
Intended accrual Control arm	3000 WBRT 50–50.4/25–28# plus boost to tumour bed up to 60–66.4 Gy	1170 WBRT 50 Gy/25#/5 weeks plus 10 Gy/5# boost to tumour bed	1935 WBRT	824 WBRT 50 Gy/25#/5 weeks plus 10 Gy/5# boost to tumour bed	2232 WBRT
Randomised comparison arm/arms	Institutional preference allocation to: 3 DCRT 38.5 Gy/10#/1 week or HDR interstitial implant 34 Gy/10#/1 week or MammoSite 34 Gy/10#/1 week	Institutional preference allocation to: 32 Gy in 8 fractions bd or 30.1 Gy in 7 fractions bd or PDR to 50 Gy 0.6–0.8 Gy h ⁻¹	Randomised to: arm 1 partial breast 40 Gy/15# with WBRT 36 Gy/15# or arm 2 partial breast 40 Gy/15#	21 Gy to 90% isodose 3–12 MeV single IO fraction	1 × 5 Gy at 1 cm 50 kV single IO fraction (20 Gy at applicator surface)
Recruiting countries	USA, Canada	Europe	UK	Milan, Italy	UK, Germany, Italy, USA, Australia
Trial features	1–3 LN positive and lobular pathology accepted		Surgical clips tumour bed	1–3 LN positive accepted	

bd, twice daily; 3DCRT, three-dimensional conformal radiation therapy; #, fraction; HDR, high dose rate; LN, lymph node; WBRT, whole-breast radiotherapy; IO, intra-operative, LN, lymph nodes, #, fractions.

The challenge of running trials in this group of patients with naturally low rates of recurrence, and thus low event rates, is clear. Very large patient numbers are needed, which can be difficult to achieve with the variety of techniques available. This may mean that studies are powered to achieve confirmation of equivalence rather than superiority.

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